REMARKS

Claims 1, 2, 4, 5, 9-18, and 42-61 are pending. Claims 3, 6-8 and 19-41 were cancelled previously. However, Applicants reserve the right to pursue the cancelled claims in a divisional or continuation application(s), if not rejoined in the instant application upon allowance.

Applicants thank the Examiner for reconsidering and withdrawing the finality of the rejections made in the Final Office Action mailed September 20, 2005, making the instant Action non-final.

In the present Non-Final Office Action, the Examiner has set forth several new rejections on the pending claims for lack of novelty and obviousness under 35 U.S.C. § 102(b) and 103(a), respectively. Applicants respectfully submit, however, that these new rejections are overcome in view of the arguments presented herewith.

Claim Rejections under 35 U.S.C. §102(b)

In the Office Action, the Examiner rejected claims 1, 2, 4-5 and 17-18 under 35 U.S.C. § 102(b) as being anticipated by U. S. Patent No. 4,931,498 to Pidgeon (hereinafter "Pidgeon"). In particular, the Examiner, while referring to independent claim 1, asserted that Pidgeon "teaches supports having a pellicular coating formed from a polyamine, such as polyethylene (column 6, lines 15-30) upon which biological membranes are immobilized (column 6, lines 32-50)." Also, the Examiner contended that Pidgeon "teaches that the membranes can remove endotoxins from contaminated protein samples (column 13, lines 1 -5)." This rejection is respectfully traversed since Pidgeon fails to describe the features set forth in independent claim 1, as well as the rejected claims depending therefrom.

Independent claim 1, as recited, is directed to a method for detecting and identifying a toxin in a sample which includes (1) providing an array comprising a plurality of biological membranes associated with a surface of a substrate, wherein the surface comprises a coating of an amine-presenting molecule and the biological membranes are deposited directly to the coating; (2) contacting the array with a solution comprising a target compound; and (3) monitoring for binding activity of at least one biological membrane with the target

compound. Support for the claimed features can be found at least on, *e.g.*, pages 3-5 and 8-13 (paragraphs 13, 41-42 and 45). Pidgeon neither teaches nor suggests deposition of biological membranes directly to a coating of an amine-presenting molecule. Accordingly, Applicants respectfully submit that Pidgeon utterly fails to anticipate claim 1, particularly in light of the additional remarks provided hereinbelow.

Pidgeon, as its title suggests, is directed to an immobilized membrane composition adapted for chromatographic systems, which include the following elements: (1) a particulate support material; (2) an artificial membrane structure; and (3) a means for immobilizing the membrane structure on the surface of the support material (col. 21-22 and claim 1). The "means" for immobilizing the membrane structure on the surface of the support material includes divalent functional groups covalently bonded to the surface of the support material and to the amphiphilic molecules forming the membrane structure (col. 22 and claim 2). As set forth in Pidgeon, "the preferred covalently immobilized membrane chromatographic supports in accordance with this invention can be accomplished by utilizing a novel phospholipid carboxylates derived by reaction of C_{10}-C_{16} cyclic dicarboxylic acid anhydrides with glycerol-phosphates and lysophospholipids" (col. 3, ll. 5-10 and col. 9, ll. 10-16). The covalently-bound artificial membranes, as set forth in Pidgeon, are illustrated in Figures 4 and 5 and further discussed in detail in the specification text (col. 8, l. 31 to col. 11, l. 64).

According to Pidgeon, the cyclic anhydride of 15-ring member cyclic anhydride represented by Formula II (at col. 9) can be used as a source of a divalent linker in the production of immobilized membranes, wherein the linker itself is used to distance the membrane forming molecules from the support surface to provide a more "bilayer-like" immobilized membrane structure. (col. 11, ll. 27-36). The covalently-bound immobilized structures were described as comparable to one-half of a biological membrane bi-layer bound to the support surface.

Thus, to fully construct a full membrane bi-layer using a cyclic anhydride as a divalent linking group between the support surface and the membrane forming amphiphilic molecules, an immobilized membrane composition, as summarized by Pidgeon, at col. 11, ll. 42-58, is prepared by the following steps: "(1) react Nucleosil-300(7NH_2) with, for example a cyclic dicarboxylic anhydride of the Formula II wherein n is 14 to provide a support material having a surface of covalently bound carboxy groups some 16-18 carbon atoms

(including carbon atoms in the propylamine group) from the surface of the support structure; (2) react the product supports with 1,1-carbonyldiimidazole to form the corresponding imidazolide; (3) reacting the imidazolide-bearing support material with an excess (to minimize crosslinking) of ethylenediamine so that the linker can on the surface of the Nucleosil-300($7NH_2$) is represented by a group of the formula -$CH_2CH_2CH_2NHCO(C_2)_{1-2}$-$CONHCH_2H_2CH_2$; and (4) reacting the Product with. For example, the lecithin imidazolide prepared in the example below" (for additional details, see col. 15, l. 64-col. 20, l. 7).

Accordingly, as per Pidgeon, a biological membrane (*i.e.*, an artificial membrane structure) cannot be directly deposited to a coating of an amine-presenting molecule (*i.e.*, supporting material) without the inclusion of the immobilization means. As a consequence, the biological membranes employed in Pidgeon cannot be directly deposited to a coating of an amine-presenting molecule.

In contrast, the method recited in clam 1 of the present invention employs a biological membrane, which is directly deposited to an amine-coated surface. As described in paragraphs 41 and 42 of the present application, this direct deposition may increase the surface resistance to physical desorption and improve the membrane's long-range lateral fluidity.

In view of the above, Applicants respectfully submit that Pidgeon fails to disclose or suggest the subject matter set forth in claim 1 of the present invention, and, therefore, does not anticipate or render obvious claim 1. Similarly, Applicants respectfully submit that Pidgeon also fails to anticipate or render obvious dependent claims 4, 12, 13, and 16-24.

In addition, claims 57 and 60-61 stand rejected under 35 U.S.C. § 102(b), as being anticipated by U. S. Patent No. 6,699,719 to Yamazaki *et al.* (hereinafter "Yamazaki"), a reference previously cited.

Claim 57 was previously rejected by the Examiner as being obvious over Yamazaki (see Office Action mailed September 20, 2005), alternatively, further in view of U. S. Patent No. 6,150,103 to Ness *et al.* or U. S. Patent No. 5,741,462 to Nova *et al.*, respectively. Based on the Applicants' arguments, filed in the Appeal Brief dated May 22, 2006, the Examiner had withdrawn these obviousness rejections. Similarly, Applicants' arguments were presented in response to the Final Office Action mailed December 20, 2005 and were based

on the ground that "Yamazaki fails to teach or suggest the elements of claim 57," which recites "a plurality of biological membranes directly deposited to a coating on a surface of said array" and "said coating comprises an amine-presenting molecule or a silane" (Applicants' Response to Final Office Action dated December 20, 2005, at ¶2, ll. 1-4, and Appeal Brief dated May 22, 2006, at ¶4, ll. 1-4), alone and in combination with the secondary references. In addition, Applicants also stated that "the bilayer membrane employed in Yamazaki is separated from the supporting surface by an aqueous film and, therefore, is not deposited directly to a coating of amine-presenting or silane molecules" (Applicants' Response to Final Office Action dated December 20, 2005, at ¶2, ll. 5 -7 and Appeal Brief dated May 22, 2006, at ¶4, ll. 5-7). Again, these deficiencies of Yamazaki applied whether alone or in combination with the now withdrawn secondary references. In view of the above, Applicants respectfully submit that Yamazaki fails as an anticipatory reference because it does not teach or suggest all of the recited elements of claim 57.

Applicants, therefore, respectfully submit that the §102(b) rejection of claim 57, as well as claims 60 and 61 dependent therefrom, be reconsidered and withdrawn. Furthermore, Applicants respectfully submit that claims 57, 60 and 61 are not rendered obvious in view of Yamazaki, as argued numerous times in prior Responses herein.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw all of the novelty rejections based upon §102(b) .

Claim Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 4-5, 9-16, 18, 42-50, 52, 54, 56 and 58-59 stand rejected under 35 U.S.C. §103(a) as being unpatentable for being obvious over Yamazaki and in view of Pidgeon, both as set forth hereinabove. Applicants respectfully traverse the rejection.

With respect to claims 1, 42, 52, 54, 56, and 58-59, the Examiner asserted that "Yamazaki teaches biosensor arrays comprising substrates with a plurality of distinct membranes of bilayer regions (column 7, lines 40-50)" and that these arrays "are performed by incubating the arrays with a cholera toxin (column 31, lines 65-67), followed by washing (column 32, lines 1-3) and imaged with a fluorescence microscope (column 32, lines 5-10). However, as noted by the Examiner, Yamazaki "does not teach membranes deposited on an amine-presenting molecule." To cure this deficiency, the Examiner cites Pidgeon which,

according to the Examiner, teaches "a surface coated with a layer of polyamine such as polyethylenimine (PEI) for attaching membranes (column 6, lines 32-50)" and that the functional groups such as PEI form covalent bonds with amphiphilic compounds and allow for mechanically stable structures" (Office Action at page 4, ¶2).

Applicants respectfully submit that both Yamazaki and Pidgeon fail to suggest the present invention, as set forth in independent claims 1, 42, and 49 and claims dependent therefrom. For example, claim 1 recites "said surface comprises a coating of an amine-presenting molecule, and said biological membranes are deposited directly to said coating." Claims 42 and 49 recite "said surface comprises a coating of an amine-presenting molecule, and each of said biological membrane microspots comprises a biological membrane directly deposited to said coating." Claim 57, which was not cited by the Examiner in this rejection but is the generic claim for rejected dependent claims 58 and 59, recites "a plurality of biological membranes directly deposited to a coating on a surface of the array" and "wherein said coating comprises an amine-presenting molecule or silane."

As noted hereinabove and in various prior filed Responses, Yamazaki fails to disclose or suggest the use of biological membranes directly deposited to a coating of amine-presenting molecules, as set forth in the claims of the present invention. Yamazaki does, however, describe the fabrication of arrays of fluid bilayer membranes, but the bilayer membranes employed in Yamazaki are separated from the supporting surface by "an aqueous film of corresponding thickness" (col. 8, ll. 1-11). This aqueous film can be made of "a buffered saline solution (*e.g.*, PBS)" and can be "readily changed (taking care, of course, to keep the supported bilayer submerged at all times) by, *e.g.*, flow-through rinsing with a solution having a different composition" (col. 10, ll. 4-9). Accordingly, Applicants respectfully submit that the primary reference cited, Yamazaki, fails to disclose or suggest the direct deposition of biological membranes to a coating of amine-presenting molecules.

Applicants respectfully submit that the proposed combination with Pidgeon fails to cure the many deficiencies of Yamazaki as a primary reference. As discussed earlier, a biological membrane (*i.e.*, artificial membrane structure), as disclosed or suggested by Pidgeon, cannot be directly deposited to a coating of an amine-presenting molecule (*i.e.*, supporting material) without the use of an immobilization means. Accordingly, any biological membranes employed in Pidgeon, as with those in Yamazaki, are not directly

deposited to a coating of an amine-presenting molecule and the combination fails to suggest the present invention, as claimed.

Because Yamazaki and Pidgeon neither disclose nor suggest elements of the claimed invention, e.g., claims 1, 42, 49 and 57, as well as any of the claims depending therefrom, Applicants respectfully submit that the primary and secondary references do not render these claims obvious. *See* MPEP §2143.03 ("To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art").

In addition to the individual and combined failure of Yamazaki and Pidgeon, Applicants respectfully submit that the primary reference, Yamazaki, teaches away from the invention as claimed in claims 1, 42, 49, and 52, as well as the claims dependent therefrom. In particular, Yamazaki describes that a thin polymer film (*e.g.*, polyacrylamide or dextran) can be deposited to an array surface to form bilayer-compatible regions, and that this thin polymer film can be coupled to the array surface by 3-methacryl-oxypropyl-trimethoxy-silane (col. 18, ll. 20-29). By not depositing bilayer membranes directly to 3-methacryl-oxypropyl-trimethoxy-silane, Yamazaki implicitly teaches that direct deposition of bilayers to silane is undesirable. Accordingly, Applicants respectfully submit that Yamazaki teaches away from the techniques set forth in the present invention, particularly the methods recited in claims 1, 42, 49, and 52.

Applicants also respectfully submit that the Examiner has failed to establish any motivation to combine Yamazaki and Pidgeon. The Federal Circuit has repeatedly emphasized that evidence of a motivation to combine must accompany a challenge based on multiple references. *See* In re Dembiczak, 175 F.3d 994 (Fed. Cir. 1999) and ATD Corp. v. Lydall, Inc., 159 F.3d 534 (Fed. Cir. 1998). *See also* MPEP §2143.01 (The prior art must suggest the desirability of the claimed invention). As the Federal Circuit observed, the "case law makes clear that the best defense against the subtle but power attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." See In re Dembiczak, 175 F.3d 994, 998-999 (Fed. Cir. 1999).

On page 4, the Office Action contends that "it would have been obvious to one of ordinary skill in the art for the support to have a layer of PEI in the method of Yamazaki *et al* to bind membranes, as suggested by Pidgeon, in order to produce mechanical stable support

structures for binding membranes." However, Applicants respectfully submit that a mere statement, that the combination of the prior art meets the claimed invention and would have been within the ordinary skill in the art, is not alone sufficient to establish a *prima facie* case of obviousness. *See* MPEP §2143.01 (emphasis added). Accordingly, Applicants respectfully request that the Examiner provide documentary proof to substantiate the alleged motivation to combine Yamazaki and Pidgeon. Moreover, as noted above, Yamazaki contemplates the use of a thin polymer film, which is coupled to the array surface by 3-methacryl-oxypropyl-trimethoxy-silane. By not using 3-methacryl-oxypropyl-trimethoxy-silane for membrane deposition, Applicants respectfully submit that Yamazaki implicitly teaches away from the use of silane and other functionally similar molecules, such as PEI, for membrane deposition.

Based on all of the above reasons, Applicants respectfully submit that the Examiner has failed to establish the *prima facie* obviousness of independent claims 1, 42, 49 and 57. Reconsideration and withdrawal of the §103(a) rejection of these claims are, therefore, earnestly requested.

Because claims 2, 4-5, 9-16, 18 and 52 depend from claim 1, claims 43-48 and 54 depend from claim 42, claims 50 and 56 depend from claim 49, and claim 58 and 59 depends from claim 57, Applicants also respectfully submit that claims 2, 4-5, 9-16, 18, 43-48, 50, 52, 54, 56, 58 and 59 are also patentable over Yamazaki in view of Pidgeon, at least for the reasons set forth hereinabove. Reconsideration and withdrawal of the §103(a) rejections of these claims are also respectfully requested.

On page 6 of the Office Action, the Examiner rejected claim 17 under 35 U.S.C. §103(a), as being unpatentable for obviousness over Yamazaki, in view of Pidgeon, as above, and in further view of U. S. Patent No. 5,004,543 to Pluskal *et al.* (hereinafter "Pluskal"). Applicants respectfully traverse the rejection.

In the Office Action, at p. 6, ¶2, l. 5, the Examiner acknowledged that Yamazaki is deficient with respect to a microporous support. Likewise, Pidgeon fails to cure the deficiency. However, this deficiency, according to the Examiner, can be found in the tertiary reference. Pluskal, as asserted by the Examiner, "teaches a charge-modified, hydrophobic microporous membrane" and "further teaches that the membrane exhibits a combination of ionic and hydrophobic properties, rendering them highly effective for macromolecular

adsorption applications under a variety of conditions (col. 2, ll. 35-46)." Claim 17 depends from claim 1. As discussed above, Applicants respectfully submit that Yamazaki and Pidgeon neither disclose nor suggest the invention of claim 1. Accordingly, Applicants respectfully submit that Yamazaki and Pidgeon fail to disclose or suggest the elements of dependent claim 17.

As with the combination of Yamazaki and Pidgeon, Applicants respectfully submit that the proposed further combination with Pluskal fails to cure the deficiencies of the primary and secondary references. Pluskal relates to a hydrophobic material having a crosslinked, cationic charge-modifying coating such that the majority of the ion exchange capacity of the material is provided by fixed formal positive charge groups. Pluskal does not describe any biological membrane deposited to a coating of amine-presenting molecules. Accordingly, Pluskal is outside the purview of the present invention, particularly as set forth in claim 17.

Because Yamazaki, Pidgeon and Pluskal, either individually or in combination, fail to disclose or suggest the elements of claim 17, Applicants respectfully submit that these references do not render claim 17 obvious. *See* MPEP §2143.03 ("To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art").

Applicants also respectfully submit that the Office Action has failed to establish any motivation to combine Yamazaki, Pidgeon and Pluskal. The Federal Circuit has repeatedly emphasized that evidence of a motivation to combine must accompany a challenge based on multiple references. *See* In re Dembiczak, ATD Corp. v. Lydall, Inc., and the MPEP, as cited and quoted hereinabove.

On page 5, the Examiner relied upon Pluskal's teachings and concluded that "it would have been obvious to one of ordinary skill in the art to have a charge-modified, hydrophobic microporous membrane as the support in the method of Yamazaki *et al.* and Pidgeon, as suggested by Pluskal *et al.*, as the membrane is highly effective for macromolecular adsorption applications under a variety of conditions" (Office Action at p. 6, ¶¶2-4). However, Applicants again respectfully submit that, a mere statement that the combination of the prior art meets the claimed invention and would have been within the ordinary skill in the art, is not alone sufficient to establish a *prima facie* case of obviousness. *See* MPEP

§2143.01 (emphasis added). Accordingly, Applicants respectfully request that the Examiner provide some form of documentary proof to substantiate the alleged motivation to combine the disparate references Yamazaki, Pidgeon and Pluskal.

Based on all of the above reasons, Applicants respectfully submit that the Office Action has failed to establish the *prima facie* obviousness of claim 17. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the §103(a) rejection of claim 17.

Lastly, claims 51, 53 and 55 stand rejected under 35 U.S.C. §103(a), as being unpatentable over Yamazaki, in view of Pidgeon, and in further view of U. S. Patent No. 4,933,285 to Patton (hereinafter "Patton").

In the Office Action, the Examiner asserted that "Yamazaki teaches biosensor arrays comprising substrates with a plurality of distinct membranes of bilayer regions (column 7, lines 40-50)" and that these arrays "are performed by incubating the arrays with a cholera toxin (column 31, lines 65-67), followed by washing (column 32, lines 1-3) and imaged with a fluorescence microscope (column 32, lines 5-10). However, Yamazaki fails to teach a coating of γ-aminopropylsilane on the support. Likewise, Pidgeon fails to cure the deficiency. To remedy this deficiency, the Examiner states that the tertiary reference Patton teaches "substrates comprising coating of γ-aminopropylsilane (column 4, lines 15-20)" and that "this produces solid phases that serve to anchor reaction products to a solid phase , while permitting the unreacted reagents to be removed (column 3, lines 35-42)." Based on these statements, the Examiner concluded that Patton's teachings "would allow Yamazaki *et al.* to anchor lipid membranes to the support that have reacted with the γ-aminopropylsilane, while removing unbound lipid membranes (Office Action at page 7, lines 4-9).

Applicants respectfully submit that Yamazaki, Pidgeon and Patton, either alone or in combination, fail to render claims 51, 53, and 55 obvious. Claims 51, 53 and 55 depend from claims 1, 42 and 49, respectively. The methods recited in claims 1, 42, and 49 employ a biological membrane directly deposited to a coating of an amine-presenting molecule. None of the cited three references describes or suggests these features. Accordingly, Yamazaki, Pidgeon and Patton, either alone or in combination, do not teach or suggest each and every element of claims 51, 53 and 55. Therefore, Applicants respectfully submit that Yamazaki, Pidgeon and Patton do not render obvious claims 51, 53 and 55. *See* MPEP

§2143.03 ("To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.").

Moreover, Applicants respectfully submit that the Office Action has failed to establish a motivation to combine Yamazaki, Pidgeon and Patton. The Federal Circuit has repeatedly emphasized that evidence of a motivation to combine must accompany a challenge based on multiple references. *See* In re Dembiczak, 175 F.3d 994 (Fed. Cir. 1999) and ATD Corp. v. Lydall, Inc., 159 F.3d 534 (Fed. Cir. 1998). *See also* MPEP §2143.01 (The prior art must suggest the desirability of the claimed invention). A mere statement, that the combination of the prior art meets the claimed invention and would have been within the ordinary skill in the art, is not alone sufficient to establish a *prima facie* case of obviousness. *See* MPEP §2143.01.

Based on the above reasons, Applicants respectfully submit that the Examiner has failed to establish the *prima facie* obviousness of claims 51, 53 and 55. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the §103(a) rejection of these claims.

In light of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw all of the above-mentioned obviousness rejections based on §103(a).

Finally, Applicants respectfully submit that all of the §§102(b) and 103(a) rejections of the pending claims have been overcome. Reconsideration and withdrawal of these rejections are earnestly requested.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly solicited. A fee for three (3)-month extension of time is due for filing this response. The Commissioner is hereby authorized to charge any payment deficiency to deposit account number 19-2380 referring to attorney docket number 015275-060007.

Should the Examiner believe that anything further is desired in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' attorney of record.

Respectfully submitted,

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